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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,653	11/21/2003	Thomas P. Jerussi	4821-529-999	9144

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EXAMINER
RAE, CHARLESWORTH E

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,653	JERUSSI, THOMAS P.	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114, received 10/31/07.

Status of the Claims

Claims 41-52 are currently pending in this application and are the subject of the Office action.

Response to applicant's arguments/remarks

Rejection under 103 (claims 41-52)

Applicant contends that this rejection should be withdrawn because of the following reasons: proffers that the rejection should be withdrawn for the following reasons:

1) The combination of cited prior art references does not teach or suggest enantionerically pure (S)-didesmethylsibutramine.

2) Even if the cited references did suggest enantionerically pure (S)-didesmethylsibutramine, they clearly do not teach or suggest enantionerically pure (S)-didesmethylsibutramine for the treatment of narcolpepsy.

3) Luscombe's teaching of didesmethylsibutramine and sibutramine have similar *in vivo* activities would not have prompted those skilled in the art to investigate didesmethylsibutramine, much less enantionmerically pure (S)-didesmethylsibutramine.

4) The examiner's allegation that a clear specific definition is lacking in the instant specification for the term "enantionerically pure (S)-didesmethylsibutramine" is without merit as said term is clearly and specifically defined in the specification to mean

"substantially free of the opposite enantiomer of the compound; the examiner is invited to review the specification at page 5.

In response, it is noted that applicant's above arguments essentially reiterates arguments set forth in previous responses to Office actions. The rejection is therefore maintained for the reasons previously made of record in the Office action mailed 10/10/07 at pages 2-12.

REJECTIONS

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41 and 48-52 are rejected under 103(a) as being unpatentable over Scott et al. (Scott et al. The effects of BTS 54 505, a metabolite of sibutramine, on monoamine and excitatory amino acid-evoked responses in the dosolateral geniculate nucleus in vivo. Br. J. Pharmacol., 111:97-102 (1994), in view of Young (WO 94/00114), and in view of Harrison's Principles of Internal Medicine (1994).

The above discussion of the 103(a) rejection in connection with the Response to applicant's arguments/remarks is incorporated by reference.

Scott et al. The effects of BTS 54 505, a metabolite of sibutramine, on monoamine and excitatory amino acid-evoked responses in the dosolateral geniculate nucleus in vivo. Br. J. Pharmacol., 111:97-102 (1994). Scott et al. teach that the primary and secondary amine **metabolites of sibutramine** (i.e. BTS 54 505, or desmethylsiburamine, and BTS 54 3554, or **didesmethylsibutramine**) have a similar pharmacological profile to the parent compound in vivo, but are up to 100 fold more potent than sibutramine as monoamine uptake inhibitors in vitro (page 97, column 1, lines 11-16; see also Figure 1). Claim 41 recites the term "enantiomerically pure (S)-didesmethylsibutramine." Scott et al. also teach the *in vitro* data indicate that the pharmacological effects of subitramine *in vivo* are mainly due to the activity of its primary and secondary amine metabolites (page 97, column 1, lines 16-20). Scott et al. also disclose that tricyclic antidepressants have a number of side effects which arise from their affinity for muscarinic cholinoceptors and histamine receptors; these side effects may limit their therapeutic use in the treatment and/or prevention of NMDA-induced toxicity and neurodegeneration (page 101, column 2, last paragraph, lines 15-

21). Scott et al. further disclose that since sibutramine and its active metabolite BTS 54 505 have no significant affinity for muscarinic receptors, α1, α2, β adrenoceptors, dopamine D1 and D2 receptors, and 5-HT1 and 5-HT receptors, sibutramine and BTS 54 505 may result in fewer and less pronounced side-effects than the tricyclic antidepressants (page 101, column 2, last paragraph, lines 21-27). Scott et al. do no teach the instant method for treating narcolepsy comprising a therapeutically effective amount of *"enantiomerically pure (S)-didesmethylsibutramine."*

Young, JW (WO 94/00114) teach compositions containing **optically pure (-) sibutramine**, which possess potent activity in treating depression, obesity and weight gain, and useful in treating disorders ameliorated by inhibition of neuronal monoamine reuptake inhibitor; sibutramine inhibit the reuptake of several monoamines such as dopamine, noradrenaline, and serotonin (page 1). Young, JW teach disorders ameliorated by neuronal monoamine reuptake inhibition to include, but are no limited to, Parkinson's disease and depression (page 2, lines 2-4). In addition, Young teaches that the magnitude of a therapeutic dose of (-) sibutramine in the acute or chronic management of a disease will vary with the severity of the condition to be treated and the route of administration (page 18, line 33 to page 19, line 5). Young teach that the recommended daily dose of (-) sibutramine range from about 1 mg to about 60 mg per day (page 19, lines 5 to 9). Young also teaches that any suitable route of administration may be employed for providing the patient with an effective dosage of (-) sibutramine e.g. oral, rectal, parenteral, transdermal; dosage forms include tablets, troches, dispersions, suspsensions, solutions,

capsules, patches, and the like (page 21, lines 7-14). In addition, Young teaches that the magnitude of a therapeutic dose of (-) sibutramine in the acute or chronic management of a disease will vary with the severity of the condition to be treated and the route of administration (page 18, line 33 to page 19, line 5). Young teach that the recommended daily dose of (-) sibutramine range from about 1 mg to about 60 mg per day (page 19, lines 5 to 9). Young also teaches that any suitable route of administration may be employed for providing the patient with an effective dosage of (-) sibutramine e.g. oral, rectal, parenteral, transdermal; dosage forms include tablets, troches, dispersions, suspsensions, solutions, capsules, patches, and the like (page 21, lines 7-14). Based on the teaching of Young et al., an artisan skilled in the art at the time the instant invention was made would reasonably have predicted that enanationmerically pure (S) **didesmethylsibutramine** would exhibit the same pharmacologic profile as the parent racemic didesmethylsibitramine in view of the fact that enantiomerically pure (-) sibutramine also exhibited the same pharmacologic profile as racemic sibutramine. Young does not teach narcolepsy.

Harrison's Principles of Internal Medicine (1994) teaches that the diagnosis of narcolepsy require the presence of the "narcolepsy tetrad," consisting of 1) excessive daytime somnolence, 2) cataplexy, 3) hypnogogic hallucinations (the occurrence of vivid hallucinationatory dream imagery at sleep onset), and 4) sleep paralysis (an awareness that voluntary musculature is paralyzed coincident with the onset of sleep (page 167, 4th full paragraph). Instant claim 41 recites the term "[a] method of treating narcolepsy." Harrison's teaches that even though early

experimental studies that focused on the raphe nuclei of the brainstem appeared to implicate serotonin as the primary sleep-promoting neurotransmitter, subsequent work has demonstrated that the raphe-serotonin system may facilitate sleep but is not necessary to its expression; the extensive pharmacology of sleep and wakefulness suggests roles for other neurotransmitters as well (page 165, column 1, 3rd full paragraph). Harrison's also teaches that treatment of **narcolepsy** is symptomatic (page 167, second to last paragraph, line 1). Harrison's teaches that treatment of cataplexy, hypogogic hallucinations, and sleep paralysis require antidepressants and that the efficacy of protriptyline, the most commonly used anti-cataplectic in the United States, is limited by its anticholignergic side effects (page 167, column 2, last two paragraphs.

Based on the teaching of Scott et al. that the primary and secondary amine metabolites of sibutramine (i.e. desmethylsiburamine and didesmethylsibutramine) have a similar pharmacological profile to the parent compound in vivo, but are up to 100 fold more potent than sibutramine as monoamine uptake inhibitors in vitro, coupled with the teaching that sibutramine and BTS 54 505 may result in fewer and less pronounced side-effects than the tricyclic antidepressants, someone of skill in the art at the time the instant invention was made would have been motivated to combine the teaching of Scott et al., in view of Young, and in view of Harrison's to create a method of treating narcolepsy comprising administering to a patient BTS 54 505 or BTS 54 354. To the extent that the racemate of BTS 54 505 and BTS 54 354 comprises the instant claimed individual isomers, the instant claimed isomers are reasonably considered to be obvious

variants over the corresponding racemate because of their presence in the racemate. It would further be expected that one of the instant isomers would be more active than the other and the racemate exhibit the combined effects.

Pharmaceutically acceptable salts, or solvate, or hydrate of BTS 54 505 and BTS 54 354, the routes of administration of the instant claimed isomers are reasonably considered to be within the capabilities of the artisan of ordinary skill in the art in the absence of evidence to the contrary. Claim 48 recites the term *"wherein the (S)-didesmethlsibutramine is administered orally, mucosally, rectally, transdermally, topically or parenterally;"* claim 49 recites the term "administered orally;" claim 50 recites the term "administered parenterally;" claim 50 recites the term "administered intravenously, intramuscularly or subcutaneously;" claim 52 recites the term "wherein the solvate is a hydrate." Also, the term "therapeutically effective amount" is construed to be reasonably within the knowledge and scope of an artisan skilled in the art without the need to resort to undue experimentation. Claim 41 recites the term "therapeutically effective amount."

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant invention with a reasonable expectation of success in view of Scott et al., in view of Young, and in view of Harrison's.

Claims 42-47 are rejected under 103(a) as being unpatentable over Scott et al., in view of Young, in view of Harrison's, and further in view of Gundlah et al. (Gundlah et al. In vivo criteria to differentiate monoamine reuptake inhibitors from releasing agents:

sibutramine is a reuptake inhibitor. Pharmacology and Experimental Therapeutics, 283 (2):581-591 (1997); **electronic copy**, pages 1-18).

The above discussions of Scott et al., Young, and Harrison's are incorporated by reference.

Gundlah et al. teach that BTS 54 505 produce a dose-dependent increase in hypothalamic 5-HT following systemic administration of 1, 3, and 10 mg/kg i.p. to rats (see Methods, pages 3-4). Although Young and Gundlah et al. do not specifically teach sibutramine metabolite administered in doses of 0.1 to 60 mg per day, or the specific relative ratios of the isomers, these limitations are within the skill of the ordinary artisan in the art and are considered to constitute pharmaceutical optimization in the absence of evidence to the contrary. For example, claim 45 recites the term "wherein the amount of (S)didesmethylsibutramine administered is from about 0.1 to about 60 mg per day;" claim 46 recites the term "wherein the amount of (S)didesmethylsibutramine administered is from about 2 mg to about 30 mg per day;" while claim 47 recites the term "wherein the amount of (S)didesmethylsibutramine administered is from about 5 mg to bout 15 mg per day." The terms "wherein the (S)-didesmethylsibutramine comprises greater than about 80 percent by weight of didesmethylsibutramine as recited in claim 42;" "wherein the (S)-didesmethylsibutramine comprises greater than about 90 percent by weight of didesmethylsibutramine as recited in claim 43;" and the term "wherein the (S)-didesmethylsibutramine comprises greater than about 95 percent by weight of didesmethylsibutramine as recited in claim 44;" are reasonably construed

to be within the scope and knowledge of an artisan skilled in the art in the absence of evidence to the contrary.

Based on the teaching of Scott et al. that the primary and secondary amine metabolites of sibutramine (i.e. desmethylsiburamine and didesmethylsibutramine) have a similar pharmacological profile to the parent compound in vivo, but are up to 100 fold more potent than sibutramine as monoamine uptake inhibitors in vitro, coupled with the teaching that sibutramine and BTS 54 505 may result in fewer and less pronounced side-effects than the tricyclic antidepressants, someone of skill in the art at the time the instant invention was made would have been motivated to combine the teaching of Scott et al., in view of Young, in view of Harrison's, and further in view of Gundlah et al. to create a method of treating narcolepsy comprising administering to a patient BTS 54 505 or BTS 54 354.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant invention with reasonable predictability.

Newly applied rejection

Claim rejections – 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 41-52 are rejected under 35 U.S.C. § 112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 41-52 are directed to encompass undisclosed "solvate and hydrate" compounds which only correspond in some undefined way to specifically instantly disclosed chemicals. None of the undisclosed solvate/hydrate compounds meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the disclosed chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

19 December 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER